



PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: DIETER HELDMANN ET AL.  
SERIAL NO.: 10/785,627 GROUP: 1626  
FILED: FEBRUARY 24, 2004  
TITLE: PROCESS FOR THE ELECTROPHILIC SUBSTITUTION OF  
THIAZOLIDINES OR OXAZOLIDINES

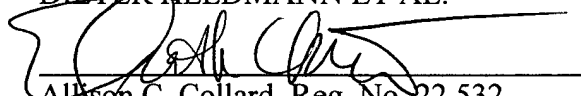
**SUBMISSION OF INFORMATION DISCLOSURE**  
**STATEMENT OF DR. ROBERT FRÄNKEL**

MAIL STOP NON-FEE AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Applicants wish to bring to the attention of the Patent Examiner the attached Information Disclosure Statement, duly signed by Dr. Robert Fränkel, and the references listed on the enclosed Form PTO-1449 and attached thereto. It is respectfully requested that the foregoing Information Disclosure Statement be incorporated into the official file of the present patent application.


Respectfully submitted,  
DIETER HELDMANN ET AL.

  
Allison C. Collard, Reg. No. 22,532  
Edward R. Freedman, Reg. No. 26,048  
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Encs: Information Disclosure Statement of Dr. Robert Fränkel, German Office Action,  
PTO-1449 form and nine (9) references

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on May 25, 2004.

  
Maria Guastella



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of  
HELDMANN ET AL.

Serial Number 10/785,627

Filed: February 24, 2004

For: PROCESS FOR THE ELECTROPHILIC SUBSTITUTION OF THIAZOLIDINES OR  
OXAZOLIDINES

Group Art Unit: 1626

Information Disclosure Statement

Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir or Madam:

I, Robert Fränkel, associated with the preparation and prosecution of the above-identified application, residing at Krottenkopfstr. 10, 81377 München, Germany, wish to call the attention of the Patent Examiner to the references enumerated on the enclosed PTO Form-1449.

I believe the documents enumerated on the enclosed Form PTO-1449 and attached thereto, are cited in the enclosed application and in the Office Action of the German Patent and Trademark Office and may be material to the examination of the application.

Therefore, it is respectfully requested that the foregoing Information Disclosure Statement be considered by the Examiner and incorporated into the file of this application.

I wish to comment as follows concerning the prior art references enumerated on PTO Form-1449:

Seebach et al., Tetrahedron Letters, 1984, vol. 25, no. 24, pages 2545-2548, cited in the application, is already in the English language.

Seebach et al., Helvetica Chimica Acta, 1987, vol. 70, pages 1194-1216, cited in the application, is already in the English language.

G. Pattenden et al., Tetrahedron Letters, 1993, vol. 49, no. 10, pages 2131-2138, cited in the application, is already in the English language.

G. Mulqueen et al., Tetrahedron, 1993, vol. 49, no. 24, pages 5359-5364, cited in the application, is already in the English language.

WO 01/72702, cited in the application and the German office action, is already in the English language.

WO 01/72703, cited in the application, is already in the English language.


Seebach et al., Angew. Chem. 1988, 100, pages 1685-1715, cited in the application, is in the German language and is a review article on structure and reactivity of lithium enolates as of 1988. The chemistry of lithium enolates is used to demonstrate that complex structures held

together by noncovalent bonds (supramolecules) may dramatically influence the result of seemingly simple standard reactions of organic synthesis. Detailed structural data have been obtained by crystallographic investigations of numerous Li enolates and analogous derivatives. The most remarkable features of these structures are aggregation to give dimers, tetramers, and higher oligomers, complexation of the metal centers by solvent molecules and chelating ligands, and hydrogen-bond formation of weak acids such as secondary amines with the anionoid part of the enolates. The presence in nonpolar solvents of the same supramolecules has been established by NMR-spectroscopic, by osmometric, and by calorimetric measurements. The structures and the order of magnitude of the interactions have also been reproduced by ab-initio calculations. Most importantly, supramolecules may be product-forming species in synthetic reactions of Li enolates. A knowledge of the complex structures of Li enolates also improves our understanding of their reactivity. Thus, simple procedures have been developed to avoid complications caused by secondary amines, formed concomitantly with Li enolates by the common methods. Mixtures of achiral Li enolates and chiral Li amides can give rise to enantioselective reactions. Solubilization by LiX is observed, especially of multiply lithiated compounds. This effect is exploited for alkylations of N-methylglycine (sarcosine) CH<sub>2</sub> groups in open-chain oligopeptides. Thus, the cyclic undecapeptide cyclosporine, a potent immunosuppressant, is converted into a THF-soluble hexalithio derivative (without epimerization of stereogenic centers) and alkylated by a variety of electrophiles in the presence of either excess lithiumdiisopropyl amide or of up to 30 equivalents of lithium chloride. Depending on the nature of the LiX additive, a new stereogenic center of (R) or (S) configuration is created in the peptide chain by this process. A structure-activity correlation in the series of cyclosporine derivatives thus available is discussed.

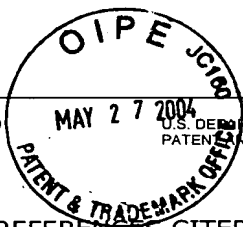
Protecting Groups, P.J. Kocienski, Thieme Verlag, 1994, pages 185-243, cited in the application, is already in the English language.

Protecting Groups, P.J. Kocienski, Thieme Verlag, 1994, pages 118-154, cited in the application, is already in the English language.

Signed this 3<sup>rd</sup> day of March, 2004.



.....  
Dr. Robert Fränkel

FORM PTO-1449  
(REV. 7-80)U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY. DOCKET NO: Co 10221

SERIAL NO. 10/785,627

## LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

APPLICANT: HELDMANN ET AL.

FILING DATE: 02/24/04

GROUP: 1626

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AL	WO 01/72702	10/4/2001	PCT				
	AM	WO 01/72703	10/4/2001	PCT				
	AN							
	AO							
	AP							

## OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	AR		Seebach et al., Tetrahedron Letters, 1984, vol. 25, no. 24, pages 2545-2548
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EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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